

Case Report

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Nivolumab Induced A Rapid Onset of Diabetes Mellitus in Patients With Cancer: Three Case Reports

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ABSTRACT

Background: Immune checkpoint inhibitors (CPIs) have been proven to be effective in terms of the response rate and survival of cancer patients. However, these drugs are responsible for several immune related adverse events (irAEs). Among the endocrine irAEs, anti-programmed cell death 1 antibodies have mostly been associated with thyroid dysfunction and recently with many cases of diabetes mellitus (DM). We report three cases of DM induced by Nivolumab with similar clinical onsets but different laboratory and presentation timings.

Cases: Of the three patients, two had a diagnosis of advanced melanoma and one of metastatic lung cancer. In all three cases, DM arose suddenly, with polyuria, polydipsia and weight loss. In two patients, DM occurred 16 and 20 months after the first Nivolumab injections without a known pancreatic autoimmunity, while in one patient, DM developed earlier after 8 weeks with detectable blood anti-glutamate decarboxylase and anti-tyrosine phosphatase 2 antibodies. All patients started insulin therapy for the rapid exhaustion of the β -pancreatic cells. In two patients, Nivolumab was temporarily stopped and immediately restarted after obtaining a good glycaemic control. In one patient Nivolumab was terminated definitively due to severe and frequent hypoglycaemias. Two cases showed thyroid dysfunction before DM onset.

Conclusions: Nivolumab induces a new form of DM which has similarities with the known Type 1 DM, but with a different pathogenesis that still remains unclear. A rapid recognition of symptoms and the correct management are fundamental in treating this medical emergency, where possible preventing the complete suspension of CPI treatment.

KEYWORDS

immune checkpoint inhibitors, cancer, diabetes mellitus, immunotherapy, immune-related adverse events, nivolumab, endocrine adverse events

INTRODUCTION

Check Point Inhibitors (CPIs) improve the response rate and survival in patients with a broad variety of haematological and solid malignancies, and have become an established treatment in oncology.¹ CPIs regulate T cell activity and facilitate the host's immune response against cancer, acting on several immune pathways.

Anti-PD-1 monoclonal antibodies, such as Nivolumab and Pembrolizumab, target PD-1 on the T-lymphocytes surface and block the inhibition of T-cell proliferation, thus reactivating the immune system against tumour cells.¹ A generalized impairment of "self-tolerance" is therefore established, triggering Immune-Related Adverse Events (irAEs). The endocrine irAEs described during anti-PD1 and anti-PDL-1 treatment are mainly thyroid dysfunction and very occasionally diabetes mellitus (DM).² The prevalence of CPI-induced diabetes mellitus (CPI-DM) reported in the literature differs from 0.2%³ up to 2%.^{4,5} however the extension of CPI treatment in several types of cancer and their long-term administration should lead to more evidence.

The onset of CPI-DM is usually strongly symptomatic, as it is characterized by weight loss, polyuria, polydipsia and, in most cases, by Diabetic Ketoacidosis (DKA).^{4,6} This clinical presentation is caused by a severe insulin deficit confirmed by undetectable C-peptide values, and requires a lifelong Multi-Dose Insulin (MDI) daily regimen.^{5,6} Although all these features make CPI-DM very similar to type 1 diabetes (T1DM), CPI-DM shows less frequent pancreatic autoimmunity positivity, and a non-typical genetic profile HLA loci.^{5,6} In addition, subjects with known type 2 DM (T2DM) on oral antidiabetic drugs may also develop CPI-DM. Indeed, patients with well-controlled T2DM can suddenly develop very high blood glucose and undetectable C-peptide values, requiring immediate MDI treatment, with or without positivity of pancreatic autoimmunity.^{4,7} Another rare form of CPI-DM in the context of Autoimmune Generalized Lipodystrophy (AGL) has also been described.^{8,9} AGL is a rare disease, thought to be immune-mediated, and characterized by significant loss and

dysfunction of subcutaneous adipose tissue with low levels of leptin, leading to severe insulin resistance with DM, hypertriglyceridemia, and non-alcoholic steatohepatitis. Overall, in terms of accurate diagnosis and management, we believe that CPI-DM should be considered as a new form of diabetes.

Here we describe three different cases of CPI-DM in cancer patients treated with nivolumab with rapid and unpredictable onset due to a severe impairment of pancreatic β -cell.

CASE REPORTS

Case 1: In May 2015, a 73-year-old man underwent surgery for a lesion in the left preauricular region. Histological examination detected a BRAF-V600K mutated amelanocytic melanoma on a lentigo maligna (0.9 mm thick according to the Breslow scale). Based on this diagnosis the man underwent a total body Computed Tomography (CT) screening showing initially no signs of disease. In February 2016, at a follow-up CT scan, a single liver metastasis was detected and surgically removed. Subsequently in May 2016 a new radiological exam revealed multiple laterocervical lymph node metastases. Immunotherapy, as the first line of treatment, was therefore proposed and immediately started with Nivolumab 240 mg every other week. At baseline, the patient had a normal Body Mass Index (BMI: 23.2 Kg/m²), and normal plasma glucose (90 mg/dL, reference range (rr): 70-100 mg/dL), sodium (139 mEq/L, rr: 135-145 mEq/L), potassium (4.3 mEq/L, rr: 3.5-4.5 mEq/L), creatinine (0.74 mg/dL, rr: 0.5-1.2 mg/dL) and TSH (0.84 μ U/mL, rr: 0.21-4.75 μ U/mL) levels. He had no previous personal or family history of DM or autoimmune diseases. Initially, the immunotherapy was well tolerated, without adverse events.

Fifteen months after the beginning of the nivolumab therapy, fasting glucose levels started rising from 105 mg/dL at the 32nd to 139 mg/dL at the 33rd drug injection (Figure 1). At the 34th cycle, the patient started complaining of lethargy, polyuria and polydipsia, associated with rapid weight loss (7 Kg in 3 weeks) and he was immediately hospitalized. Laboratory tests revealed acute kidney injury (creatinine: 1.9 mg/dL, rr: 0.5-1.2 mg/dL) and DKA characterized by severe hyperglycaemia (726 mg/dL, rr: 70-100 mg/dL), hyperkalemia (5.5 mEq/L, rr: 3.5-4.5 mEq/L), glycosuria (>1000 mg/dL), and ketonuria (60 mg/dL). Further investigation showed HbA1c levels of 84 mmol/mol and normal pancreatic enzymes (amylase: 25 U/L, rr: 13-53 U/L; lipase: 47 U/L, rr: <67 U/L) with no signs of pancreatic inflammation or neoplastic infiltration at abdominal CT. Nivolumab treatment was therefore temporarily suspended, and fluids and insulin were immediately administered according to the classical approach to DKA. After the acute phase, basal-bolus subcutaneous insulin treatment was set up.

DM autoimmunity evaluated at the time of the diagnosis showed negative Anti-Glutamate Decarboxylase (anti-GAD), Anti-Insulin (IAA)

Case 1

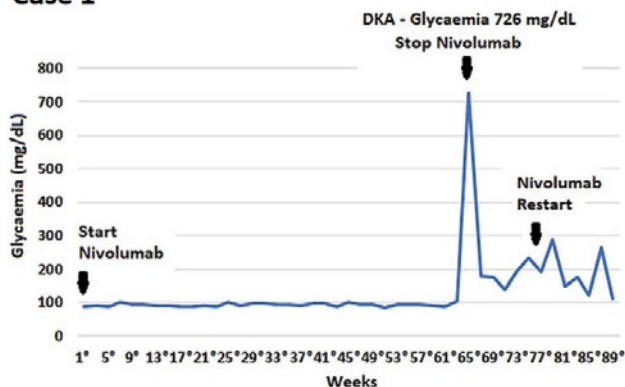


FIGURE 1 Beginning of the nivolumab therapy, fasting glucose levels.

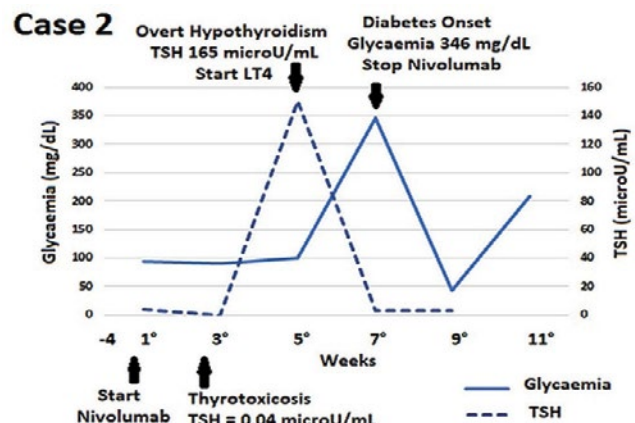


FIGURE 2 Laboratory investigations performed before nivolumab therapy showed normal thyroid function.

and Pancreatic Anti-Insula (ICA) antibody titers. The same tests were repeated six months later, confirming the negative antibody profile. Nevertheless, an extremely low C-peptide value (0.4 ng/mL; rr: 0.9-7.1 ng/mL) was found, supporting the immuno-mediated genesis of DM. The genetic profile of the patients was also assessed, showing an HLA-DRB1*10,*11 genotype.

Once optimal glycaemic control had been achieved with insulin administration (after an overall suspension treatment period of 98 days), Nivolumab therapy was started again, maintaining good metabolic control.

At the last radiological check (at 169 weeks of Nivolumab treatment), the disease was stable, and the patient was still under insulin therapy. No other endocrine abnormalities were detected. In particular, the pituitary and thyroid function were within the normal range.

Case 2: In June 2012, a 52-year-old woman underwent a middle-upper right bilobectomy and mediastinic lymphadenectomy for a moderately differentiated G2 lung adenocarcinoma, Epidermal Growth Factor Receptor (EGFR) and Anaplastic Lymphoma Kinase (ALK) wild type. Due to cancer pleural invasion, the patient started chemotherapy with carboplatin and gemcitabine followed by local radiotherapy. In February 2013, at a chest CT scan follow-up, a contralateral lung metastasis was found and an enucleoresection was performed. At the beginning of 2017, a brain CT scan revealed secondary lesions and the patient started an anti-edema treatment with dexamethasone (Soldesam® 0.2% 96 drops/die). A few months later, new lung and liver metastases were found and in April of the same year, the immunotherapy protocol with Nivolumab (150 mg every other week) was initiated.

The patient reported no previous personal or family history for autoimmune diseases or DM. Her BMI was 19.5 Kg/m² and laboratory investigations performed before nivolumab therapy showed normal thyroid function (TSH: 1.9 microU/mL, rr: 0.55-4.78 microU/mL) and plasma glucose (75 mg/dL, rr: 70-100 mg/dL), despite dexamethasone administration (Figure 2).

Six weeks after the beginning of nivolumab treatment (3rd cycle), blood tests revealed a reduction in TSH (0.04 microU/mL, rr: 0.55-4.78 microU/mL) with normal ft3 (2.58 pg/mL, rr: 2.3-4.2 pg/mL) and ft4 (14.6 pg/mL, rr: 8.9-17.6 pg/mL) levels. The patient was asymptomatic thus no treatment was started, however the thyrotoxicosis progressed to overt hypothyroidism over an 8-week period (TSH: 150 microU/mL, rr: 0.55-4.78 microU/mL; ft4: 3.0 pg/mL, rr: 8.9-17.6), requiring lifelong levothyroxine therapy. An anti-thyroid autoimmunity profile was performed, showing marked positivity for anti-thyroglobulin (173 U/mL, rr: <15 U/mL) and anti-thyroperoxidase (331 U/mL, rr: <35 U/mL), while no anti-TSH

receptor antibodies were detected (0.28 U/L; rr: <0.55 U/L). Neck ultrasound showed a hypoechoic and markedly irregular thyroid gland, suggestive of thyroiditis.

After the 4th cycle of nivolumab, the patient complained of polydipsia and polyuria. The blood tests showed hyperglycaemia (glucose: 346 mg/dL) and high HbA1c levels (66 mmol/mol), suggestive of DM (Figure 2). Amylase values were normal (15U/L; n.v. < 53 U/L) and an abdominal CT scan found no signs of pancreatic inflammation or metastases. The pancreatic autoimmunity profile showed positive anti-GAD (22.82 U/mL; rr: <28 U/mL) and anti-IA2 (20.65 U/mL; rr: <5 U/mL), but undetectable ICA levels (<1.4 U/mL; rr: <20 U/mL), thus supporting the autoimmune pathogenesis of DM.

The patient was immediately treated with an MDI regimen, while Nivolumab and dexamethasone were stopped.

Despite training the patient to insulin therapy and the use of a continuous blood glucose monitoring system, the patient never achieved an adequate glycaemic control. In fact, there was considerable variability in blood glucose values and frequent hypoglycaemic episodes. At the follow-up CT scan, cancer progression was detected and Nivolumab was completely terminated.

In this case, we were not able to perform a genetic profile due to the patient's worsening clinical condition and progression of the disease.

Case 3: In June 2015, a 52-year-old woman was diagnosed with metastatic uveal melanoma and treated firstly with 3 mg/kg of Ipilimumab every 3rd week (four administrations) and subsequently with Nivolumab i.v. 240 mg every 2nd week.

She had a normal weight (BMI: 21.5 kg/m²) and reported no personal or family history of DM. At baseline before Nivolumab was administered, glucose levels were in the normal range (82 mg/dL, rr: 70-100 mg/dL).

Fifteen weeks after nivolumab initiation (3rd cycle), the patient developed thyrotoxicosis (TSH: 0.03 microU/mL, rr: 0.25-4.5 microU/mL; fT3: 3.8 pg/mL, rr: 2.5-4.5 pg/mL; fT4: 10.2 pg/mL, rr: 5.5-12 pg/mL), which in only four weeks developed into overt hypothyroidism (TSH: 61.01 microU/mL, rr: 0.25-4.5 microU/mL; fT3: 2.4 pg/mL, rr: 2.5-4.5 pg/mL; fT4: 2.7 pg/mL, rr: 5.5-12 pg/mL), requiring lifelong levothyroxine therapy. The anti-thyroid autoimmunity profile was negative (anti-thyroglobulin <1 U/mL, rr: <5 U/mL; anti-thyroperoxidase <5 U/mL, rr: < 9 U/mL; with anti-TSH receptor antibodies <0.3 U/L, rr: < 1 U/L). Neck ultrasound imaging was suggestive of thyroiditis with reduced vascularization of the gland.

Eighty weeks after nivolumab administration (35th cycle), the patient started complaining of polydipsia and polyuria. At clinical evaluation, a weight loss of 4 kg was observed and a laboratory blood glucose level of 292 mg/dL and HbA1c of 53 mmol/mol were found

(Figure 3). The C-peptide values were initially inadequately normal despite the high glycaemia (1.2 ng/mL; rr: 0.9-7.1 ng/mL), but after a few months they became undetectable. The autoimmune profile showed negative anti-GAD and ICA antibodies, and the genetic analysis revealed an HLA-DRB1*11,*16 haplotype.

MDI treatment was immediately started and a good glycaemic profile was rapidly achieved. Nivolumab treatment was temporarily suspended, but resumed after 53 days.

At the last radiological check-up (162 weeks after starting CPI), melanoma appeared stable on nivolumab treatment and insulin therapy was still ongoing with a good glycaemic control.

DISCUSSION

The three cases reported above demonstrate the extreme variability in the timing of CPI-DM onset with mild-to severe clinical presentation, but all requiring lifelong insulin treatment. According to our data, the onset of CPI-DM can both occur after a few CPI administrations and after several CPI cycles without clear warning signs. Similar data have been reported describing CPI-DM cases after only one CPI administration.¹⁰⁻¹² On the other hand, Wright et al.¹³ in the Vigibase[®] cohort observed many late onset cases, even after the suspension of CPIs, thus highlighting the need for continuous glycaemic monitoring.

Interestingly, when we evaluated the time of onset of CPI-DM and the presence of pancreatic autoimmunity, we found pancreatic autoantibodies positivity in the early onset case and none in the later ones. These data seem to confirm previous studies that found cases of rapid onset CPI-DM with positive pancreatic autoimmunity.^{11,12,14}, and with others characterized by undetectable pancreatic antibody titers after a long period of treatment.¹⁵⁻¹⁹ However, an isolated case, reported by Tsang et al.⁵, showed a positive anti-GAD in late onset CPI-DM. Nevertheless, we cannot rule out other unknown immune-response mechanisms involved besides the classical pancreatic autoimmunity which is probably only marginally involved in the CPI-DM pathogenesis.

Stamatouli et al.³ followed the antibody profile in three patients that developed CPI-DM, from before the first CPI administration to the onset of CPI-DM, and detected different trends. In particular, one patient had negative anti-GAD, anti-IA2 and anti-Zn8T at baseline and after treatment, whereas the second subject presented positive antibodies both before and after the therapy, and the third patient had a positive seroconversion of anti-GAD and anti-IA2 antibodies. Interestingly, this study reported that 25% of patients on treatment with CPIs who did not develop CPI-DM, had positive anti-GAD antibodies.³

Therefore, although it is likely that CPIs cause positive anti-GAD antibodies, other factors are probably required in the pathogenesis of CPI-DM supporting its difference from T1DM. Moreover, unlike T1DM, in which positive antibodies are found in over 80% of subjects, in CPI-DM positive antibodies are present in about half of the cases.

In two of our cases, which were both female, CPI-DM was preceded by thyroiditis which evolved into overt hypothyroidism requiring replacement levothyroxine treatment. One patient showed negative thyroid autoimmunity and the other patient was positive. Surprisingly, the same patient with detectable anti-GAD and anti-IA2 antibodies also showed positive thyroid autoimmunity. Although the role of pancreatic antibodies is still questionable, we cannot rule out a possible predisposition to autoimmune disease in some subjects and not in others.

Considering the known association of T1DM with some HLAs, in particular DR4, we investigated the genetic profile of two of our three cases of CPI-DM. Although an association has been found between HLA-DR4 and CPI-DM,³ the known protective HLA genotypes for

Case 3

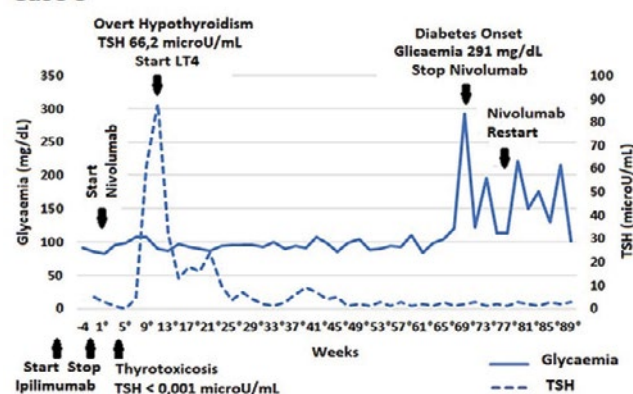


FIGURE 3 Clinical evaluation after nivolumab administration.

T1DM onset did not show the same result for CPI-DM.⁵ In fact, also in our cases, both patients with late onset CPI-DM showed a T1DM protective HLA, highlighting that CPI-DM has a different pathogenesis compared to T1DM. As for the autoimmune profile, it is possible that HLA-DR4 is associated with early onset CPI-DM, but not with late onset which showed a different HLA association.

The common feature between CPI-DM and T1DM is the sudden clinical and dangerous onset. In our cases, as also described in the literature, at the time of diagnosis, the blood glucose values were always very high occasionally with DKA and low levels of C-peptide. These data suggest an extremely acute onset based on the very rapid loss of pancreatic β -cell function. The evolution of C-peptide during CPI-DM has been found to become undetectable within 15 days of CPI-DM onset and this deficiency is persistent, requiring lifelong insulin therapy.²⁰⁻²² Moreover, unlike many irAEs, steroid therapy does not appear to improve pancreatic inflammation in CPI-DM.

Two studies evaluated the administration of high-doses of cortisone aimed at stopping β -cell destruction, both showing persistent low C-peptide levels and unmodified CPI-DM requiring lifelong insulin administration.^{23,24} In addition, the use of steroids for other adverse events in cancer patients did not change the evaluation of CPI-DM, confirming the ineffectiveness of steroid therapy.^{18,25} However, three male cancer patients with CPI-DM have also been described, in which C-peptide levels were preserved and insulin therapy became obsolete after some months.²⁶⁻²⁸ A possible explanation for at least one patient was the concomitant administration of Infliximab for oligoarthritis affecting the right knee and both ankles.²⁸ In fact, Infliximab is a α -TNF inhibitor and is likely to reduce pancreatic inflammation resulting in a possibly better CPI-DM outcome. Infliximab was also used in eighteen pediatric patients newly diagnosed with T1DM, which led to an improvement in C-peptide loss.²⁹

These data on the effects of infliximab are still hypotheses and no studies to date have analysed the α -TNF levels in CPI-DM. However, it would be extremely interesting to examine this hypothesis further.

Although CPI-DM is always sudden, some patients have shown a slight increase in glycaemia in the weeks preceding DKA onset, as we observed in case #1. During this short period, an oral antidiabetic drug was used.^{7,30,31} Lee et al.³² administered gliflozin in the weeks preceding DKA onset, which probably contributed to the subsequent onset of DKA.

The fact oral antidiabetic drugs are not effective may be due to the rapid destruction of β -pancreatic cells, which quickly results in overt insulin deficiency. In fact, it is very important to intercept these very early stages of CPI-DM in order to perform further investigations (i.e. C-peptide levels, pancreatic autoantibodies and genetic profile) and to immediately start the right therapy.

When CPI-DM occurs with DKA, the suspension of CPIs is appropriate³³ because it is a grade 3 irAE according to the Common Terminology Criteria for Adverse Events (CTCAE), but to date none of the guidelines express an opinion regarding the possible restarting of CPIs, once DM control has been achieved. This decision is therefore guided by the cancer response, by the presence of other side effects and the general clinical conditions. In some cases, such as our case #2, CPI-DM became extremely difficult to control and the disease was progressing, and thus it was decided to stop the CPI treatment.

Considering the sudden and potentially dangerous onset of CPI-DM, all the guidelines agree on the importance of monitoring the glycaemic values serially during CPI therapy.³³ In the case of CPI interruption, the continued monitoring of blood glucose values seems valid due to the late onset of CPI-DM even after immunotherapy discontinuation.

It is also essential that patients are adequately informed

regarding the symptoms, in particular polyuria and polydipsia, in order to be able to quickly recognize DM. Finally, C-peptide values and pancreatic autoimmunity need to be immediately assessed in patients who develop blood glucose alterations in order to start adequate therapy. Patients with CPI-DM who do not quickly achieve good metabolic compensation should be rapidly equipped with continuous blood glucose monitoring systems in order to resume immunotherapy as soon as possible, if appropriate.

CONCLUSIONS

CPI-DM is an emerging type of autoimmune DM which shares some aspects with T1DM but should be considered differently. CPI-DM can occur early or after many months of therapy, or sometimes even after CPI has been stopped. Generally, CPI-DM appears with overt symptomatology (polydipsia, polyuria, weight loss, vomiting), with very high blood glucose values and frequently with DKA. C-peptide levels are very low from early stages and positive autoantibodies are present in half of patients. Unlike other irAEs, CPI-DM does not improve with steroid therapy and lifelong replacement insulin therapy is almost always required.

There are currently no predictive clinical or biochemical parameters for CPI-DM. The most important tool is to train patients to recognize DM symptoms early and to periodically monitor blood glucose values. If even slight changes in blood glucose values occur, further analyses need to be conducted immediately to identify the most suitable therapy, which generally consists of insulin replacement therapy. The achievement of a good metabolic compensation is essential to resume the CPI treatment as soon as possible.

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REFERENCES

1. Ribas A. Tumor immunotherapy directed at PD-1. *N Engl J Med*. 2012;366(26):2517-2519.
2. Cukier P, Santini FC, Scaranti M, Hoff AO. Endocrine side effects of cancer immunotherapy. *Endocr Relat Cancer*. 2017;24(12):T331-T347.
3. Stamatouli AM, Quandt Z, Perdigoto AL, Clark PL, et al. Collateral Damage: Insulin-Dependent Diabetes Induced With Checkpoint Inhibitors. *Diabetes*. 2018;67(8):1471-1480.
4. Kotwal A, Haddox C, Block M, Kudva YC. Immune checkpoint inhibitors: an emerging cause of insulin-dependent diabetes. *BMJ Open Diabetes Res Care*. 2019;7(1):e000591.
5. Tsang VHM, McGrath RT, Clifton-Bligh RJ, Scolyer RA, et al. Checkpoint inhibitor-associated autoimmune diabetes is distinct from type 1 diabetes. *J Clin Endocrinol Metab*. 2019;104(11):5499-5506.
6. Clotman K, Janssens K, Specenier P, Weets I, et al. Programmed cell death-1 inhibitor-induced type 1 diabetes mellitus. *J Clin Endocrinol Metab*. 2018;103(9):3144-3154.
7. Wright LAC, Ramon RV, Batacchi Z, et al. Progression to insulin dependence post-treatment with immune checkpoint inhibitors in pre-existing type 2 diabetes. *AACE Clin Case Rep*. 2017;3:e153-e157.
8. Falcao CK, Cabral MCS, Mota JM, Arbache ST, et al. Acquired lipodystrophy associated with nivolumab in a patient with advanced renal cell carcinoma. *J Clin Endocrinol Metab*. 2019;104:3245-3248.

9. Jehl A, Cugnet-Anceau C, Vigouroux C, Legeay AL, et al. Acquired generalized lipodystrophy: a new cause of anti-pd-1 immune-related diabetes. *Diabetes Care*. 2019;42(10):2008-2010.
10. Miyauchi M, Toyoda M, Zhang J, Hamada N, et al. Nivolumab-induced fulminant type 1 diabetes with precipitous fall in C-peptide level. *J Diabetes Investig*. 2020;11(3):748-749.
11. Zezza M, Kosinski C, Mekoguem C, Marino L, et al. Combined immune checkpoint inhibitor therapy with nivolumab and ipilimumab causing acute-onset type 1 diabetes mellitus following a single administration: two case reports. *BMC Endocr Disord*. 2019;19(1):144
12. Gunjur A, Klein O, Kee D, Cebon J. Anti-programmed cell death protein 1 (anti-PD1) immunotherapy induced autoimmune polyendocrine syndrome type II (APS-2): a case report and review of the literature. *J Immunother Cancer*. 2019;7(1):241.
13. Wright JJ, Salem JE, Johnson DB, Lebrun-Vignes B, et al. Increased reporting of immune checkpoint inhibitor-associated diabetes. *Diabetes Care*. 2018;41(12):e150-e151.
14. Akturk HK, Alkanani A, Zhao Z, Yu L, et al. PD-1 inhibitor immune-related adverse events in patients with preexisting endocrine autoimmunity. *J Clin Endocrinol Metab*. 2018;103(10):3589-3592.
15. Hatakeyama Y, Ohnishi H, Suda K, Okamura K, et al. Nivolumab-induced acute-onset type 1 diabetes mellitus as an immune-related adverse event: a case report. *J Oncol Pharm Pract*. 2019;25(8):2023-2026.
16. Dehghani L, Mikail N, Kramkimel N, Soyer P, et al. Autoimmune pancreatitis after nivolumab anti-programmed death receptor-1 treatment. *Eur J Cancer*. 2018;104:243-246
17. Fukui A, Sugiyama K, Yamada T, Tajitsu M, et al. A case of nivolumab-induced fulminant type 1 diabetes with steroids and glucagon-like peptide 1 administration during the early onset. *J Clin Case Rep*. 2016;11:1-3.
18. Sakaguchi C, Ashida K, Yano S, Ohe K, et al. A case of nivolumab-induced acute-onset type 1 diabetes mellitus in melanoma. *Curr Oncol*. 2019;26(1):e115-e118.
19. Maekawa T, Okada K, Okada H, Kado S, et al. Case of acute-onset type 1 diabetes induced by long-term immunotherapy with nivolumab in a patient with mucosal melanoma. *J Dermatol*. 2019;46(12):e463-e464.
20. Okamoto M, Gotoh K, Masaki T, Ozeki Y, et al. Fulminant type 1 diabetes mellitus with anti-programmed cell death-1 therapy. *J Diabetes Investig*. 2016;7(6):915-918.
21. Matsumura K, Nagasawa K, Oshima Y, Kikuno S, et al. Aggravation of diabetes, and incompletely deficient insulin secretion in a case with type 1 diabetes-resistant human leukocyte antigen DRB1*15:02 treated with nivolumab. *J Diabetes Investig*. 2018;9(2):438-441.
22. Yamamoto N, Tsurutani Y, Katsuragawa S, Kubo H, et al. A patient with nivolumab-related fulminant type 1 diabetes mellitus whose serum c-peptide level was preserved at the initial detection of hyperglycemia. *Intern Med*. 2019;58(19):2825-2830.
23. Chae YK, Chiec L, Mohindra N, Gentzler R, et al. A case of pembrolizumab-induced type-1 diabetes mellitus and discussion of immune checkpoint inhibitor-induced type 1 diabetes. *Cancer Immunol Immunother*. 2017;66(1):25-32.
24. Smith-Cohn MA, Gill D, Voorhies BN, Agarwal N, et al. Case report: pembrolizumab-induced Type 1 diabetes in a patient with metastatic cholangiocarcinoma. *Immunotherapy*. 2017;9(10):797-804.
25. Villarreal J, Townes D, Vrablik M, Ro K. A case of drug-induced severe endocrinopathies: what providers in the emergency department need to know. *Adv Emerg Nurs J*. 2018;40(1):16-20
26. Marchand L, Thivolet A, Dalle S. Diabetes mellitus induced by PD-1 and PD-L1 inhibitors: description of pancreatic endocrine and exocrine phenotype. *Acta Diabetol*. 2019;56:441-448.
27. Hansen E, Sahasrabudhe D, Sievert L. A case report of insulin-dependent diabetes as immune-related toxicity of pembrolizumab: presentation, management and outcome. *Cancer Immunol Immunother*. 2016;65:765-767.
28. Trinh B, Donath MY, Läubli H. Successful treatment of immune checkpoint inhibitor-induced diabetes with infliximab. *Diabetes Care*. 2019;42:153-154.
29. Mastrandrea L, Yu J, Behrens T, Buchlis J, et al. Etanercept treatment in children with new-onset type 1 diabetes: pilot randomized, placebo-controlled, double-blind study. *Diabetes Care*. 2019;32:1244-1249.
30. Kong AH, Lee SY, Yang YS, Kim TM, et al. Anti-programmed cell death 1 therapy triggering diabetic ketoacidosis and fulminant type 1 diabetes. *Acta Diabetol*. 2016;53:853-856.
31. Sothornwit J, Phunmanee A, Pongchaiyakul C. Atezolizumab-induced autoimmune diabetes in a patient with metastatic lung cancer. *Front Endocrinol*. 2019;10:352.
32. Lee S, Morgan A, Shah S, Ebeling PR. Rapid-onset diabetic ketoacidosis secondary to nivolumab therapy. *Endocrinol Diabetes Metab Case Rep*. 2018;2018:18-21.
33. Thompson JA, Schneider BJ, Brahmer J, Andrews S, et al. NCCN guidelines insights: management of immunotherapy-related toxicities, version 1.2020. *J Natl Compr Cancer Netw JNCCN*. 2020;18(3):230-241.